


EXHIBIT 21

NEWS AND VIEWS

Talc powder and ovarian cancer: what is the evidence?

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Abstract

Talc is a desiccant that has been historically used as baby powder by numerous women to enhance their feminine hygiene. Talc has been identified in proximity to asbestos; accordingly, retrospective and case-control studies have implicated the role of talc use in the development of ovarian cancer, whereas prospective evaluations have not documented concordant findings. Moreover, the positive associations derived from case-control studies have been remote and the putative causal factors remain inconclusive. Consequently, one should be circumspect regarding the assertion that genital talc powder application induces ovarian cancer development.

Keywords Talc use · Ovarian cancer · Risk factors · Prevalence

Introduction

Ovarian cancer is the most aggressive gynecologic malignancy in the United States, contributing to 14,000 deaths annually [1]. The neoplasm potentially manifests itself in response to hereditary factors, including BRCA1 and BRCA2 gene mutations, which potentially increase a woman's lifetime risk of the disease by approximately 50% and 30%, respectively [2]. Additionally, case-control studies have implicated talc powder as a risk factor in ovarian carcinogenesis [3–5].

Talc is frequently used as a desiccant in hygienic or cosmetic agents. Talc was initially purported to be carcinogenic because the silicate is encountered adjacently to asbestos and quartz [6], two minerals notoriously associated with malignancies [7, 8]. Asbestos's carcinogenic mechanism is postulated to be the protein, HMGB1, which initiates an inflammatory process that induces neoplastic infiltration [9].

When silicates were originally detected in body powder, there was speculation that talc powder was contaminated by asbestos from mining-related procedures [10, 11]. Talc powder was further considered a contributory factor in ovarian cancer in response to findings indicating that asbestos

precipitated ovarian tumor development in guinea pigs [12]. Thenceforth, a case-control study asserted that perineal talc use was associated with an increased risk for ovarian cancer [4].

Mechanism of action

The primary mechanism for talc-induced ovarian cancer is reproductive tract inflammation, a response putatively engendered by talc particulate migration and embedment in ovarian epithelial tissue [13, 14]. Consequently, increased oxidative stress levels, DNA damage, and cell division are prompted, whereupon carcinogenesis is theoretically occasioned [15]. However, perineal application of talc does not conclusively render vaginal or cervical permeation, much less ovarian infiltration [16, 17]. Similarly, the contention that talc fibers migrate into the diaphragm via the peritoneal cavity and ultimately pervade the ovaries is quite speculative [18]. Nevertheless, there have been rare, histopathologic cases of talc identified in the lymph nodes, cervix, uterine corpus, and fallopian tubes via polarized light and scanning electron microscopy [19].

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Clinical evidence

Several case–control studies have examined the relationship between talc use and ovarian cancer development, wherein an elevated risk (relative risk: 1.1–3.9) of developing ovarian cancer was reported [5, 20–22], whereas alternative reports have not demonstrated a relationship [4]. Despite the select assertions from these case–control studies that talc use contributes to ovarian cancer development, both prior and subsequent talc exposure to a cancer diagnosis was assessed, thereby confounding the rates between case and control subjects [13]. There was also profound study variability involving the application of talc (e.g., diaphragm, sanitary napkin, condom) and the specific exposure areas (e.g., genital, perineal) [8, 15], not to mention long-term recall bias inherent in self-reported measures [6].

In a prospective, pooled-data study conducted by the National Institute of Health, 252,745 women reported on their talc powder frequency of use and duration [23]. The primary outcome measures were ever use of powder on the genitalia and incidence of ovarian cancer. Following a duration of 11.2 years, the study findings recounted an ovarian cancer incidence of 61 cases/100,000 (0.061%) for users and 55 cases/100,000 (0.055%) for never users, a difference that was not statistically significant. Similarly, another prospective analysis from the Nurses' Health Study examined talc use and the development of ovarian cancer with 78,630 female registered nurses [24]. The results indicated no overall association with talc use and a risk for ovarian cancer (multivariate relative risk = 1.09; 95% CI = 0.86–1.37), irrespective of talc application frequency.

Discussion

Initially, ovarian cancer development was predicated on the exposure of asbestos to talc, two silicates that are naturally occurring. While talc products may have contained asbestos, cosmetic talc has been asbestos-free for several decades [6]. In May 2020, Johnson and Johnson discontinued their talc-based baby powder and thus, proponents of talc powder's carcinogenic attributes should eventually predict a decrease in ovarian cancer incidence. However, there has already been a steady decline in ovarian cancer for nearly 30 years; since 1992 to 2019, the observed rate of new annual ovarian cancer cases in the United States fell from 14.9/100,000 (0.0149%) persons to 9.6/100,000 (0.0096%) [1]. Perhaps, since talcum powder use has declined significantly since the 1990s [25], a

decreased incidence in ovarian cancer incidence might be attributed to talc-free latex condoms, but lead-time bias and an imprecise duration of oncogenesis preclude any irrefutable determination.

Conclusion

While several case-control studies have suggested a relationship between talc powder and the incidence of ovarian cancer, numerous epidemiological studies have refuted any such association. Since clinical research has accorded inconsistent findings, an implicated biomarker for talc powder and ovarian carcinogenesis has not been elucidated, and confounding variables have been insufficiently addressed, an unequivocal conclusion that the observed associations between talc powder and ovarian cancer are causal remains untenable [13]. Nevertheless, in endeavoring to attenuate potential health risks, researchers should further evaluate the effects of both prolonged exposure and specific timing (i.e., opportunistic circumstances) of talc use to conclusively determine if the silicate harbors carcinogenic potential.

Author contributions JPM: conceptualization, supervision, original draft preparation, and final review. MAR: content analysis, draft preparation, and final manuscript review. RB: reviewed content, participated in draft preparation, and final review. BHG: study supervision, original draft preparation, final editing, and study approval.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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